FORM PTO-1390 (REV 3/2001)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

DATE: **September 10, 2001**

EXPRESS MAIL LABEL NO.
EL717377563US

ATTORNEY DOCKET NO.
47237/DBP

U.S. APPLICATION NO.
NA **09/936576**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/CN00/00041	**March 2, 2000**	**March 9, 1999**

TITLE OF INVENTION
PHARMACEUTICAL COMPOSITION CONTAINING CYCLOSPORIN

APPLICANT(S) FOR DO/EO/US
ZHANG, Yonghua

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (UNEXECUTED)
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 13 to 20 below concern document(s) or other information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A FIRST preliminary amendment..
16. ☐ A SECOND or SUBSEQUENT preliminary amendment..
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ SMALL ENTITY Assertion: Applicant(s) and any other associated with it/them under 37 CFR § 1.27(a) are a small entity.
20. ☒ Certificate of Mailing by Express Mail.
21. ☒ Other items or information: Extra Set of Drawings

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NO.
N/A 09/936576	PCT/CN00/00041	47237/DBP

21. The following fees are submitted:	CALCULATIONS	PTO USE ONLY
☒ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO: **$1,000.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 1,000	
Surcharge of **$130** for furnishing the oath or declaration later than ☐20 ☒30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130	

Claims	Number Filed	Number Extra	Rate		
Total Claims	13 -20=	0	X $18	$	
Independent Claims	1 -3=	0	X $80	$	
Multiple dependent claim(s) (if applicable)			+ $270	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1,130	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 1,130	
Processing fee of **$130** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 1,130	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property				$	
TOTAL FEES ENCLOSED =				$ 1,130	
Note (1): The basic national fee must be paid when filing this application. The 20-month time limit (37 CFR § 1.494) and 30-month time limit (37 CFR § 1.495) are not extendable.				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$ 1,130.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No._____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **03-1728**. A duplicate copy of this sheet is enclosed.

NOTE (2): Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

D. Bruce Prout
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CUSTOMER NUMBER: 23363

By D Bruce Prout
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Reg. No. 20,958

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXPRESS MAIL NO. EL717377563US

Applicant	:	Yonghua Zhang
Application No.	:	N/A
Filed	:	September 10, 2001
Title	:	PHARMACEUTICAL COMPOSITION CONTAINING CYCLOSPORIN
Docket No.	:	47237/DBP/C306

PRELIMINARY AMENDMENT

Post Office Box 7068
Pasadena, CA 91109-7068
September 10, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

Commissioner:

Please amend the above-identified application as follows:

IN THE SPECIFICATION

After the title please add the following:

-- CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority of International application number PCT/CN00/00041, filed March 2, 2000, which in turn claims priority to Chinese patent application number 99102848.1, filed March 9, 1999--.

REMARKS

It is respectfully requested that the foregoing preliminary amendment be entered prior to examination

Respectfully submitted,

CHRISTIE, PARKER & HALE, LLP

By _____
D. Bruce Prout
Reg. No. 20,958
626/795-9900

DBP/aam

AAM PAS378618 1-*-9/10/01 9 09 AM

Title

Pharmaceutical Composition containing cyclosporin

Field of the invention

The present invention relates to a pharmaceutical composition comprising a cyclosporin as an active ingredient; a solvent or co-surfactant such as ethanol or propylene glycol or mixture thereof; as solubilizer a hydrophilic surfactant having HLB value of 10-19;as lipophilic component one or a mixture of two or more selected from the group consisting of pharmaceutical organic acids such as medium/long chain saturated or unsaturated fatty acid and substituted carboxylic acid, or fish oil;and where appropriated, water for making hydrophilic substrate being present or absent. The composition may be formulated into soft capsule, ointment, eye-drop, oral solution, injection and so on.

More particularly, the invention relates to a composition comprising cyclosporin which is insoluble in water. The composition may be formulated into many formulations, such as soft capsule, ointment, eye-drop, oral solution, injection and so on. In accordance with the present invention, here is provided information about the each component.

Background

The active ingredient is cyclosporin, also known as cyclosporin A or ciclosporine. It is a cyclic polypeptide consisting of 11 amino acids. Cyclosporin has now been as a novel and efficient immunosuppressive agent in the clinic field, especially in the prevention of organ rejection following

organ and bone marrow transplantation and the therapy of various autoimmune diseases. It acts in the early lymphocyte proliferation phase and the action of inhibition for cell is reversible. In additional, It doesn't affect hematopoietic function of bone marrow and not cause to decrease of amount of WBC and RBC. Cyclosporin is white crystal powder which has molecular weight of 1202.64. It's highly hydrophobic and sparingly water-soluble ,and as well dissolved in an organic solvent such as methanol, ethanol, acetone, ether, chloroform and the like. Due to above-mentioned reasons, cyclosporine oral solution is poor absorbed and has low bioavailability. In the 1980's, the scientists of Sandoz Company dissolved cyclosporin with ethanol, then formulated an oil form in junction with vegetable oil and Labrafil M 1944CS having HLB value of 3. After added some water in the formulation, the composition become unstable and turbid. The sandoz's formulation containing cyclosporin is thus generally administered with dilution of milk or fuit juice. The bioavailability of said formulation depends on the patent's body condition, individual difference etc. The variation of bioavailability is in the range of about 4-60%. Therefore, it is very difficult for said formulation to retain an effective therapeutic concentration of Cyclosporin. Further, the primary side effects of cyclosporin are hepatotoxic and nephrotoxic. With the dosage increasing, said side effect become more serious. Furthermore, the evaporation of ethanol during the preparation process and the storage of the soft capsule over time may also result in the precipitation of cyclosporin contained in the formulation, whereby bioavailability levels and stablility of cyclosporin are decreased.

In order to improve the bioavailability of Cyclosporin, reduce the marked difference in the individual and the inconvenience of diluting with milk or juice before the oral cyclosporine solution is administrated, numerous studies have been extensively conducted to discover an novel preparation suitable for cyclosporin well -distribution in the water with molecular state, which make

absorption of cyclosporin not be affected by bile and the fat in food. Accordingly, Sandoz Company has marketed a preparation of cycloprine in the form of a emulsion pre-concentrate which trademark as SANDIMUN NEORAL and Korea-America Pharmaceutical Company has also marketed a preparation of cycloprine in the form of a emulsion pre-concentrade which trademark as IMPLANTA.

Object of the invention

The object of the present invention is to develop a liquid composition which enable the stability of cycloprine more higher.

The inventors of the present invention have studied about various surfactant, co-surfactaaant, solubilizar, and oil ingredient based on the research of solubilization for insoluble drugs and find a new liquid composition comprising cyclosporin, which is never disclosed in the prior art. The present composition has many advantages such as improvement stability and no-influence with co-surfactant migration during the preparation process and the storage period , even when exposed or opened or in water-existing condition, it may still exhibit more stability than the known preparation. The ratio of cyclosporin as an active ingredient is in the range of 0.5-15% by weight based on the weight of composition.

Within the range , the composition is in the best emulsified state. Thus, the new oral preparation containing cyclosporine in the present invention has great improvement on bioavailability than those of the prior art,and has the same bioequivalence with said Sandimmun Neoral on the market.

Summary of the present invnetion

The present invention relates to a pharmaceutical composition containing cyclosporin which comprises:

(1) cyclosporin as active ingredient;

(2) as solvent or co-surfactant ethanol, propylene glycol or mixture thereof;

(3) as solubilizer hydrophilic surfactant having HLB value from 10 to 19;

(4) as lipophilic component a pharmaceutical organic acid selected from the group consisting of saturated or unsaturated fatty acid having medium/long chain、substituted carboxylic acid or mixture thereof, or fish oil;

(5) where appropriated, presence or absence of water or hydrophilic base containing water.

The composition may be formulated into various form such as soft capsule, soft cream, eye-drop, oral solution and injection etc.

Detailed description of the present invention.

The present invention relates to a pharmaceutical composition containing cyclosporin which comprises:

(1) cyclosporin as active ingredient;

(2) as solvent or co-surfactant ethanol, propylene glycol or mixture thereof;

(3) as solubilizer hydrophilic surfactant having HLB value from 10 to 19;

(4) as lipophilic component a pharmaceutical organic acid selected from the group consisting of saturated or unsaturated fatty acid having medium/long chain、substituted carboxylic acid or mixture thereof, or fish oil;

(5) where appropriated, presence or absence of water or hydrophilic base containing water.

The composition may be formulated into various form such as soft capsule, soft cream, eye-drop, oral solution and injection etc.

According to the present invention, the solvent or co-surfactant for dissolving an insoluble drug is selected from the group consisting of ethanol, propylene glycol and the mixture thereof. The ratio of ethanol: propylene glycol is 1: 0.1-10(w/w),more preferably1: 0.5-5(w/w) and most preferably 1: 1-3(w/w).

According to the composition of present invention, the hydrophilic pharmaceutical surfactant having HLB from 10 to 19 is used as solubilizers for liposoluble drugs to achieve the balance between the hydrophilic component and the lipophilic component and form a steady emulsion. These surfactants involve, for example, the derivatives of polyoxyethylene castor oil, such as Cremophor EL, Cremophor RH40, Cremophor 60, or Tween type, such as Tween 80, Tween 65, Tween 20, and the Myrj such as Myrj 52. The derivatives of polyoxyethylene castor oil are preferred.

According to the composition of the present invention, said composition characterizes by using a pharmaceutical organic acids or fish oil as lipophilic component, wherein an organic acid is selected from the group consisting of saturated or unsaturated fatty acid having medium/long chain and substituted carboxylic acid or mixture thereof. The lipophilic component make the composition of the present invention more stable and simple than that of prior art. In the present invention, the above-mentioned carboxylic acid may be in esterfied or free form. Among the all components, the lipophilic component may be the saturated acids having medium/long chain are C_{8-28} carboxylic acid; the unsaturated acids having medium/long chain are C_{10-24} mono-, di-, or tri-olefine acid; the substituted carboxylic lactic; or the fish oil containing 70% DHA. As lipophilic component unsaturated fatty acids having the medium/long chain especially C_{14-22} mono- , di-, or tri-olefine acid are preferred.

According to the present invention, the another character of the composition of present invention lies in that water is present or absent depending on different form of each composition. The ratio of the active

ingredient to the water is in the range of 1:0-1000 by weight. For example, adding certain water in to the oral solution containing cyclosporin can cut down the temperature of solidify or forming flocculation of a composition. Accordingly, the character can be applied for the preparation of hydrophilic ointment and eye-drop.

According to the present invention, to meet the different requirement in the clinic application, the composition which contain cyclosporin or other fat-soluble drugs is formulated into soft gelatin capsule, ointment, eye-drop, oral solution, injection and so on.

Further, depending on the different requirement of the formulation, excipient or adjuvant may also be used, e.g., anti-oxidant, flavoring agent, osmosis promoter, agent for adjusting pH, antiseptic and so on, and not limited to above-mentioned range. The method of preparation of various formulations can be taken under the conventional method in the art.

The present invention will be more specifically illustrated by the following examples. However, it should be understood that the present invention is not limited by these examples in any manner.

Example 1 The preparation of CsA oral solution

INGREDIENT	QUANTITY(mg)
Cyclosporin	100
Mixture of ethanol and propylene glycol	230
Polyoxyethylene castor oil	400
Oleate	220
Vitamin E	2
Purified water	a.q.
Total	1000ml

Example 2 The preparation of CsA capsule

INGREDIENT	QUANTITY(mg)
Cyclosporin	50
Mixture of ethanol and propylene glycol	100
Polyoxyethylene castor oil	200
Refined fish oil	130
Total	1300 capsules

Example 3 The preparation of CsA eye-drop

INGREDIENT	QUANTITY(mg)
Cyclosporin	20
Mixture of ethanol and propylene glycol	50
Polyoxyethylene castor oil	90
Stearic magnesium	220
Vitamin E	1
Physiological saline	a.q.
Total	1000ml

A study on relative bioavailability was carried out by comparing the oral solution preparation prepared by the example1 (new cyclosporin oral solution, thereafter named as -New Cyspin) with the known cyclosporin soft capsule(named as Cyspinin below) and Sandimmun capsule.

A result of pharmacokinetic parameters derived from above comparision is obtained from 12 male health volunteers who received cyclosporin soft capsule (Cyspinin commercial), New Cyclosporine Oral Solutio ("New

Cyspin") provided by Hangzhou Zhongmeihuadong Pharmaceutical Co. Ltd. and the Cyclosporine capsule named as Sandimmun Neoral ("Sandimmun Neoral" is commercial available). The obtained whole-blood concentration was detected by HPLC, followed by pharmacokinetical assay according to statistic matrix, by use of 3P87 and NDST computer programs. The results showed: after oral administration of the Cyspinin, New Cyspin and Sandimmun Neoral, respectively, AUC (AUC is an area under curve of concentration of blood-drug vs time and is a main parameter for determing bioavilability in the art) were 11.43±2. 49, 16.77±2.49 and 16.39± 3.54mg/l*h, respectively; Cmax (peak valve of blood-drug concentration) were 1.56±0. 25, 2.38±0.38 and 2.47±0.42mg/l respectively; and Tmax (time for achieving peak value of blood-drug concentration) were 2.04± 0. 54, 2.00±0.56 and 1.62±0.38h respectively. The major pharmacokinetic parameters AUC, Cmax and Tmax showed: remarkable difference existed between Cysipinin and New Cyspin, Sandimmun Neoral, but no remarkable difference existed between New Cyspin and Sandimmun Neoral. The relative bioavailability of Cyspin and New Cyspin Vs Sandimmun Neoral was73.4±25.2%, 105.0±17.9%. The results of the study confirmed the bioequivalence of New Cyspin and Sandimmun Neoral in human body.

12 male health adult volunteers were selected to voluntarily receive the administration under complying with the requirement of " Guideline for Medical Preparation in Bioavailability Study Conducted on Human Body" issued by the Medical Administration Bureau of Health Ministry. Routine laboratory tests showed that their blood, urine, liver and kidney functions, electrocardiogram and related immunological indexes were normal. During the two weeks before the test and the period in test the testees were required to free from any drugs.

Cyclosporine Reference Standard, supplied by Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd. (9201C, Purity 0.976mg/mg)

Inside-label, Cyclosporin D (thereafter named as 'CSD'), purity 98.4%, supplied by *Sichuan Industrial Institute of Antibiotics* and prepared to 1.2mg/l solution for being ready.

The volunteers should not take any food from supper the day before to 4 hours after administration. There were totally 12 persons in the test, divided into 3 group, each group including 4 persons. The first group took orally CYSPIN IN 500mg, the second group took NEW CYSPIN 500mg, the tird group took Sandimmun Neoral 500mg, all taking together with 300ml of juice. The volunteers were given standard food with little fat 4 hours after administration. Each volunteer undergo Cross-administration (Cyspin ,New Cyspin & Sandimmun Neoral) one time with the interval of 7 days. Collect venous blood respectively at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 8.0, 12 and 24 hours after orally administration. Put the blood sample in the heparin-anticoagulating test tube, stored at -40℃ for determination after shaking vigorously.

The blood samples obtained were detected by direct injection method, through column conversion. 1ml of whole blood sample was transferred into a 5 ml plastic centrifugal tube with plug, followed by accurately adding 1.0 ml of CSD working solution, 1.0 ml of methanol and 1.0 ml of hexane, successively, the mixture was allowed to be vertically blended for 1 min, and then centrifuged for 10 min (1600r/min). The hexane phase in upper level was discarded while the clear solution in lower level was transferred into a 1.5 ml centrifugal tube and again centrifuged for 10min (1600r/min), 1.0 ml of the centrifuged solution was applied into the chromatography system for assay. An RP2 column (30x4.6mm, 25-40□m) was applied as the purifying column, self-filled according to homogenization method. The mobile phase for purification was a mixture of methanoland water (65:35), flow rate 1ml/min. The purification time was defined as 10min, tangential time 1min; a Shim-pack CLC-OBD column (150×6mm, 5□m) together with a pre-

column (ODS, 10×4.6mm, 10□m) were applied for separation, column temperature 70℃; the mobile phase for assay was a mixture of acetonitrile and 0.025mol/l of Sulphonamide (82:18, pH 2.5), flow rate 1ml/min, the wave length for detection was at 210nm, and sensitivity of instrument was set at 0.02 AUFS. The detected retention time of CsA and CsD were 9.2 min and 11.2 min , respectively. Quantitative assay was conducted through measuring peak height by internal standard method, and a linear range existed from 0.025-3mg/l, y=1.04×10-3x-4.06×10-3, R=0.9999 , the signal-to-noise ratio was 3, the concentration limit of whole blood was 0.01mg/l. In this range, respectively took 1.0 ml standard CsA in high, middle and low concentration, followed by adding 1.0 ml of empty whole blood sample, 1.0 ml of CSD working solution, 1.0 ml of n-hexane, successively, the mixture was allowed to be vertically blended for 1 min. According to the above-mentioned method, detected the high of CsA (H). And then took 1.0 ml standard CsA with the same concentration, adding 1.0 ml of water, 1.0 ml of CsD working solution, after being vertically blended for 1 min, directly detected the high of CsA (H0). Treated the H/H0 as purification recovery, the average purification recovery was 98.5% (Table 1`), the average method recovery was 99.3% (Table 2). Intra-day RSD was 2.3% and day-to-day RSD was 2.6% (Table 3). Figure 1 is the Curve of Mean Concentration vs. Time. In Figure 1, abscissa represents time after administration (hr), ordinate represents blood-drug concentration (mg/l), each point in trangle shows the curve of the average concentration after adminstration of sandimmun Neoral vs time, each point in square shows the curve of the average concentration after adminstration of cyspinin Neoral vs time, each point in rhomboid represents shows the curve of the average concentration after adminstration of New cyspin solution vs time.

Pharmacokinetic parameters and bioavailability F

1) The practical pharmacokinetic computer program which was used to

control 3 P87 and new medical statistic program NDST, formulated by the Chinese Society of Pharmacology, were adopted for statistic processing in a P-133 computer. 1,2 -dimensional analogue-curves of fit were conducted respectively based on variation of blood conc. The results declared: pharmacokinetic result of oral administration of New Cyspin met the 1-dimensional model. The calculation of AUC, MRT, etc. was conducted according to statistic matrix, Cmax and Tmax were obtained based on actual data of blood conc. vs time, T1/2 was calculated according to 1-dimensional model, and pair-t test was adopted for statistic processing, in which AUC of Cyspin , New Cyspin and Sandimmun Neoral were 11.43±2.48,16.77±2.49 and 16.39±3.54mg/l*h; Cmax1.56±0.25, 2.38±0.388 and 2.47±0.42mg/l; Tmax 2.04±0.54, 2.00±0.56 and 1.62±0.38h.

2) Calculation of Bioavilability (F)

F=(AUC of New Cyspin/AUC of Sandimmun Neoral)×100%

The relative bioavailability of Cysipinin and New Cyspin vs Sandimmun Neoral was 73.4±25.2%, 105.0±17.9%, calculated by average, was 69.7% and 102.3%.

Table 1. The Purification Recovery of CsA in the Whole Blood Samples (Tested by HPLC, N=5)

CsA Conc. (mg/l)	H	HO	Purification Recovery (%)	RSD (%)	Average
0.101	729	740	98.51	2.01	
0.504	3566	3641	97.95	1.83	98.51
2.018	14456	14593	99.06	1.05	

Table 2 The Method Recovery of CsA in the Whole Blood Samples (Tested by HPLC, N=5)

Adding (mg/l)	Measurement (mg/l)	Recovery (%)	Average	SD (%)
0.101	0.101	99.81		
0.504	0.496	98.41	99.31	0.64
2.018	2.012	99.70		

Table 3. The Precision of CsA in the Whole Blood Samples (Tested by HPLC)

Concentration (mg/l)	RSD (Intra-day)	Times	RSD (Day-to-day)	Times
0.102	1.76	5	1.88	3
0.505	1.48	5	2.34	3
2.070	2.27	5	2.57	3

Claim

What is claimed is:

1.A pharmaceutical composition comprising:

1) a cyclosporin as active ingredient;

2) a solvent or a co-surfactant such as ethanol, propylene glycol and the mixture of them

3) a hydrophilic surfactant having a hydrophilic-lipophilic balance (HLB) value of 10 to 19 as solubilizer;

4) lipophilic component which is one or a mixture of two or more selected from the group consisting of pharmaceutical organic acids such as medium/long chain saturated or unsaturated fatty acid and substitutive carboxylic acid, and fish oil as;

5) where appropriated, water for making the hydrophilic substrate is present or absent.

said composition is formulated into soft capsule, ointment, eye-drop, oral solution, injection, etc.

2. The composition according to claim 1 wherein said solvent or co-surfactant is ethanol, propylene glycol or a mixture of them.

3. The composition according to claim 1 wherein the ratio of said ethanol to propylene glycol is from 1:0.1 to 1:10 (w/w).

4. The composition according to claim 1 wherein the ratio of said ethanol to propylene glycol is from 1:0.5 to 1:5 (w/w).

5. The composition according to claim 1 wherein said the surfactant having the HLB value of 10 to 19 is the derivatives of polyoxyethylene castor oil, Tween, and Myrj.

6. The composition according to claim 1 wherein as the lipophilic component said medium/long chain saturated fatty acid is C_{8-28} carboxylic acid.

7. The composition according to claim 1 wherein as the lipophilic component

said medium/long chain unsaturated fatty acid is C_{10-24} mono-, di-, or tri-olefine acid.

8. The composition according to claim 1 wherein as the lipophilic component said medium/long chain unsaturated fatty acid is C_{14-22} mono- , di-, or tri-olefine acid.

9. The composition according to claim 1 wherein said substituted carboxylic acid is lactic acid .

10. The composition according to claim 1 wherein as the lipophilic component said fish oil comprises 70% DHA (w/w).

11. The composition according to claim 1 wherein said oil component is one or a mixture of two or more selected from the group consisting of pharmaceutical organic acids, such as medium/long chain saturated or unsaturated fatty acid and substituted carboxylic acid.

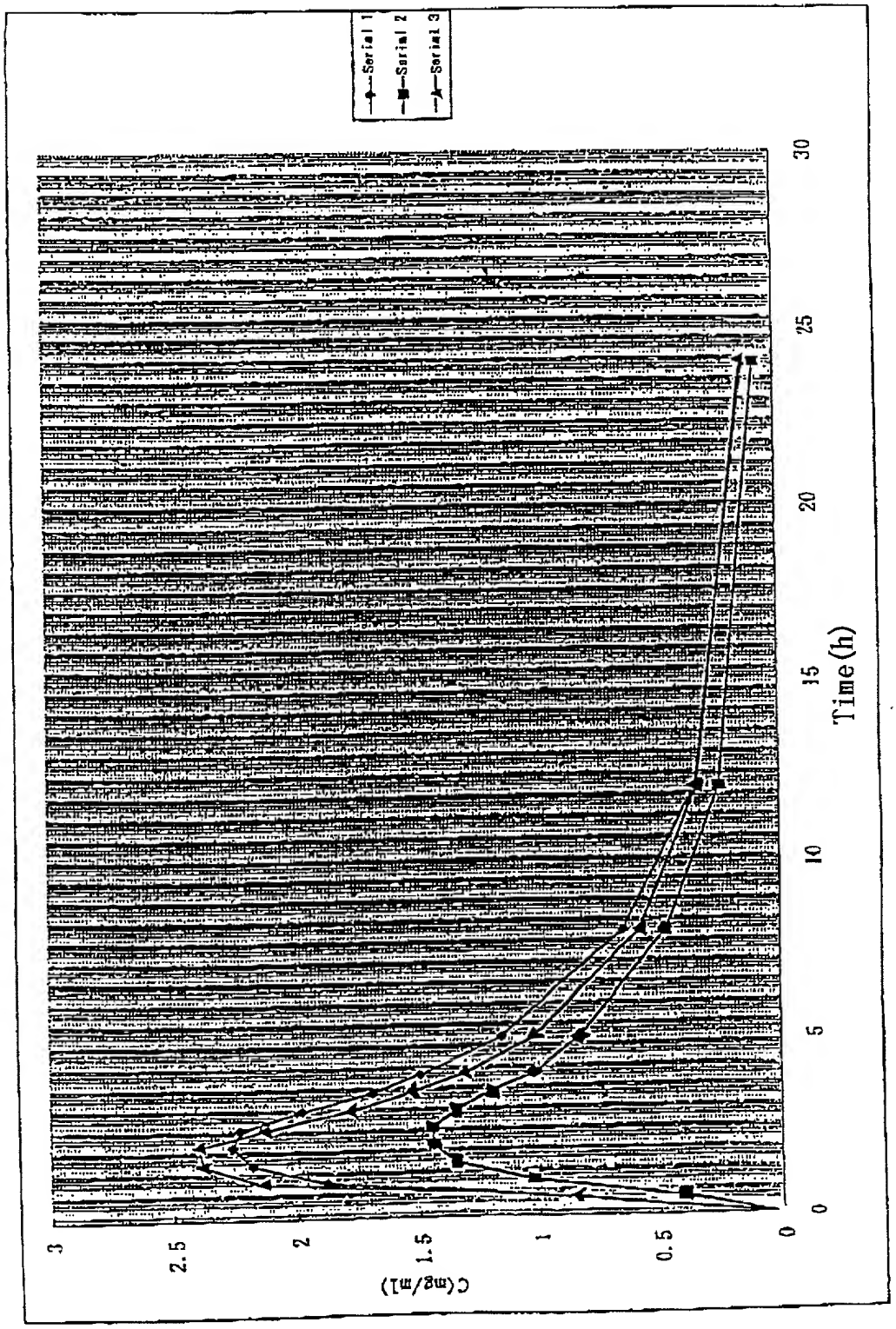
12. The composition according to claim 1 wherein said ratio of cyclosporin to the puried water is 1:0-1000. (w/w).

13. The composition according to claim 1 wherein said composition is formulated into soft capsule, ointment, eye-drop, oral solution, injection and so on.

Abstract

The present invention relates to pharmaceutical compositions comprising a cyclosporin as an active ingredient. It is characteristic of the compositions that chioce of one or a mixture of two or more selected from the group consisting of pharmaceutical organic acids, such as medium/long chain saturated or unsaturated fatty acid and substitutive carboxylic acid as lipophilic component. For the sake of satisfying the requirement of different formulations, hydrophilic substrate can be made by added proper purified water or not. The composition is suitable for soft capsules, ointments, eye-drop, oral solution, injection and so on.

Fig. 1


Serial 1
Serial 2
Serial 3
C(mg/ml)
Time(h)
0
0.5
1
1.5
2
2.5
3
0
5
10
15
20
25
30

Rev. 11/00 **DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION** PATENT

Docket No. : 47237/DBP/C306

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PHARMACEUTICAL COMPOSITION CONTAINING CYCLOSPORIN, the specification of which is attached hereto unless the following is checked:

_X_ was filed on _March 2, 2000_ as United States Application Number or PCT International Application Number _PCT/CN00/00041_ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of the foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below, any foreign application for patent or inventor's certificate, or any PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Application Number	Country	Filing Date (day/month/year)	Priority Claimed
99102848.1	China	9 March 1999	YES

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

Application Number	Filing Date	Patented/Pending/Abandoned

POWER OF ATTORNEY: I hereby appoint the following attorneys and agents of the law firm CHRISTIE, PARKER & HALE, LLP to prosecute this application and any international application under the Patent Cooperation Treaty based on it and to transact all business in the U.S. Patent and Trademark Office connected with either of them in accordance with instructions from the assignee of the entire interest in this application;

or from the first or sole inventor named below in the event the application is not assigned; or from CCPIT Patent and Trademark Law Office in the event the power granted herein is for an application filed on behalf of a foreign attorney or agent.

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I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION

Docket No. 47237/DBP/C306

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